This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1. (**Currently Amended**) A method for identifying a compound that induces a ~~morphogen-mediated~~ biological effect mediated by a morphogen selected from OP-1, OP-2, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-9, Vg1, Vgr-1, DPP, or 60A, the method comprising:

   (a) providing a test cell comprising DNA defining a ~~morphogen-responsive~~ transcription activating element responsive to said morphogen, and, in operative association ~~therewith~~ with said transcription activating element, a reporter gene encoding a detectable gene product, said DNA, when present in a ~~morphogen-responsive~~ cell responsive to said morphogen and contacted with ~~the~~ said morphogen, serving to induce transcription of said reporter gene;

   (b) exposing said test cell to a candidate compound; and

   (c) detecting expression of said detectable gene product, wherein an increase in expression of said detectable gene product after exposing said test cell to said candidate compound indicates the ability of said candidate compound to induce the morphogen mediated biological effect;

   wherein said morphogen-mediated biological effect requires the presence of said morphogen-responsive transcription activating element.

2. (**Original**) The method of claim 1 wherein said morphogen responsive transcription activating element binds with a protein having general DNA-binding properties of a MEF-2 family protein, said DNA binding inducible by performing step (b).

3. (**Previously Presented**) The method of claim 1, wherein said morphogen responsive transcription activating element comprises a sequence that hybridizes to an MEF-2 binding site sequence.

4. (**Currently Amended**) The method of claim 1 wherein said morphogen responsive transcription activating element comprises nucleotides 699-731 of ~~Seq. ID No. 1~~ SEQ ID NO: 1.

5. (**Currently Amended**) The method of claim 1 wherein said morphogen responsive transcription activating element comprises nucleotides 682-761 of ~~Seq. ID No. 1~~ SEQ ID NO: 1.

6. (**Original**) The method of claim 1 wherein said morphogen responsive transcription activating element comprises a sequence of A and T residues.

7. (**Currently Amended**) The method of claim 6 wherein the sequence of A and T residues comprises nucleotides 699-711 of ~~Seq. ID No. 1~~ SEQ ID NO: 1.

8. (**Currently Amended**) The method of claim 6 wherein the sequence of A and T residues comprises nucleotides 703-724 of ~~Seq. ID No. 1~~ SEQ ID NO: 1.

9. (**Original**) The method of claim 6 wherein the A and T residues are adjacent to an AP-1 biding site sequence.

10. (**Currently Amended**) The method of claim 9 wherein the AP-1 binding site sequence comprises nucleotides 715-724 of ~~Seq. ID No. 1~~ SEQ ID NO: 1, or the nucleotide sequence of ~~Seq. ID No. 2~~ SEQ ID NO: 2.

11-12. (**Canceled**)

13. (**Currently Amended**) A method of producing a compound competent to induce a ~~morphogen-mediated~~ biological effect mediated by a morphogen selected from OP-1, OP-2, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-9, Vg1, Vgr-1, DPP, or 60A, the method comprising:

   a. obtaining said compound by screening at least one candidate compound according to the method of claim 1 or 2; and

   b. producing said compound or a derivative thereof having substantially the same ability as said compound to induce said morphogen mediated biological effect.

14. (**Canceled**)

15. (**Currently Amended**) A method of assessing whether a sample comprises a substance competent to bind to DNA, the sequence of which comprises nucleotides 699-731 of ~~Seq. ID No. 1~~ SEQ ID NO: 1, the method comprising:

a. providing DNA, the sequence of which comprises nucleotides 699-731 of ~~Seq. ID No. 1~~ SEQ ID NO: 1;

b. exposing said DNA to said sample; and,

c. detecting the binding of said substance to said DNA.

16-29. **(Canceled)**

30. **(Currently Amended)** A method of detecting a ~~morphogen-mediated~~ biological effect mediated by a morphogen selected from OP-1, OP-2, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-9, Vg1, Vgr-1, DPP, or 60A, the method comprising detecting DNA binding of a protein that induces said morphogen-mediated biological effect, said protein having a polypeptide sequence of a morphogen-inducible DNA binding protein which can interact with nucleotides 699-711, 715-724, 699-731, 682-731, 703-724 or 682-761 of SEQ ID NO: 1.

31. **(Currently Amended)** The method of claim 30 comprising the additional step of providing ~~a~~ said morphogen or ~~a morphogen~~ analog thereof to a morphogen responsive cell prior to said detecting step, and wherein said DNA binding is detected within about 2 to 12 hours.

32. **(Currently Amended)** The method of claim 30 comprising the additional step of providing ~~a~~ said morphogen or ~~morphogen~~ analog thereof to a morphogen responsive cell prior to said detecting step, and wherein said DNA binding is detected within about 2 to 6 hours.

33. **(Original)** The method of claim 1, 2, 15 or 30 comprising part of a medium or high-flux screening assay.

34-35. **(Canceled)**

36. **(Currently Amended)** A method for identifying a candidate compound that induces a ~~morphogen-mediated~~ biological effect mediated by a morphogen selected from OP-1, OP-2, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-9, Vg1, Vgr-1, DPP, or 60A, the method comprising:

(a) providing a test cell comprising DNA defining a ~~morphogen-responsive~~ transcription activating element responsive to said morphogen, said DNA, when

present in a ~~morphogen responsive~~ cell responsive to said morphogen and contacted with ~~the~~ said morphogen, serving to induce transcription of a gene operatively associated with said transcription activating element;

(b) exposing said test cell to a candidate compound; and

(c) detecting morphogen inducible DNA binding to said transcription activating element by a cellular protein, wherein an increase in said binding after exposing said test cell to said candidate compound indicates the ability of said candidate compound to induce said morphogen mediated biological effect,

wherein step (c) occurs within approximately 2-12 hours of completing step (b), and wherein said morphogen-mediated biological effect requires the presence of said morphogen-responsive transcription activating element.

37-42. **(Canceled)**

43. **(Previously Presented)** The method of claim 1 wherein the morphogen is OP-1.

44. **(Previously Presented)** The method of claim 2, wherein said morphogen-responsive transcription activating element also binds with a second protein having general DNA-binding properties of an AP-1 family protein.

45. **(Previously Presented)** The method of claim 1, wherein the morphogen is OP-2, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, Vg1, Vgr-1, DPP, or 60A.

46. **(Previously Presented)** The method of claim 43 or 45, wherein the morphogen is of human origin.

47. **(Previously Presented)** The method of claim 1, wherein said morphogen-mediated biological effect is: stimulating proliferation of mammalian bone / cartilage progenitor cells, stimulating differentiation of mammalian bone / cartilage progenitor cells, supporting growth and maintenance of mammalian endochondrial bone tissue, delaying or mitigating the onset of senescence or quiescence-associated loss of phenotype or tissue function, stimulating phenotypic expression of differentiated cells, inducing redifferentiation of transformed cells, induction of VEGF expression, induction of PTH-mediated cAMP production in osteoblast, or induction of neuronal marker.

48. (**Previously Presented**) The method of claim 47, wherein said neuronal marker is L1 or N-CAM.

49. (**Previously Presented**) The method of claim 1, wherein said morphogen-mediated biological effect is induction of mitogenesis and phenotypic markers for chondrocyte or osteoblast differentiation.

50. (**Previously Presented**) The method of claim 49, wherein said phenotypic markers is: type I collagen, type II collagen, type X collagen, alkaline phosphatase, osteocalcin, N-cadherin, N-CAM, or MSX-2.

REMARKS

Upon entry of this amendment, claims 1-10, 13, 15, 30-33, 36, and 43-50 are pending and currently under consideration in the instant application. Claims 14, 16-29, and 37-42 are canceled without prejudice to expedite prosecution. Applicants reserve the right to prosecute claims of identical or similar scope in future applications.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Double Patenting

Claims 1-10, 13, 15, 30-33, 36, and 43-50 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Pat. No. 5,834,188. Without conceding the appropriateness of this rejection, Applicants will submit a terminal disclaimer, if necessary, to obviate this rejection upon indication of allowable subject matter.

Claim rejections under 35 U.S.C. 103(a)

Claims 1 and 13 are rejected under 35 U.S.C. 103(a), as being unpatentable over Foulkes *et al.* (U.S. Pat. No. 5,863,733) in view of Wobus *et al.* (Differentiation 48: 173-182, 1991).

The Office Action essentially reiterated the rejection in the previous Office Action verbatim. In the "Response to Arguments" section, the Office Action alleges that Applicants attempts to "narrow the meaning of the phrase 'morphogen-mediated biological effect' by arguing that it is not generic." The Office Action again points to page 19, lines 9-10 of the instant specification, and reiterates that "the claim is broadly permissive to any biological effect that is associated with any interaction of a morphogen, including the chronotropic effect disclosed by Wobus." However, there is no evidence of record whatsoever indicating that the "the chronotropic effect disclosed by Wobus" is indeed induced by a morphogen, which is the fulcrum of the current disagreement.

As Applicants stated in the response to the previous Office Action, Wobus essentially teaches that mouse ES cells can differentiate to heart muscle cells under certain *in vitro* culture conditions, and that such differentiated heart muscle cells have certain features (expressing certain cell surface receptors, capable of responding to certain cardioactive drugs, etc.). However, it is unclear what this *in vitro* culture system has to do with any morphogens. Wobus never used "morphogen" once. In addition, the Office Action never provides a single reason or any evidentiary support to show that the "the chronotropic effect disclosed by Wobus" actually has anything to do with morphogens at all. Thus, contrary to the Office Action's allegation, all the elements necessary to establish a *prima facie* case of obviousness do *not* exist.

Nevertheless, Applicants have amended claims 1, 13, 30, and 36 to further clarify the subject matter claimed. These recited morphogens were neither disclosed nor suggested by any of the cited references. Reconsideration and withdrawal of the rejection is respectfully requested.

The rejection of claims 1-3, 6, 9, 13, 30-33, 36, 43-50 on grounds of 35 U.S.C. 103(a) depends on the combined teaching of Foulkes and Wobus, further in view of Nadal-Ginard. Since Nadal-Ginard does not overcome the defect of the combined teachings of Foulkes and Wobus, the combined teachings of all three references still fail to arrive at the claimed invention in the absence of a showing that the biological effect is a "morphogen-mediated" one.

Claims 1,13, 36, 43, 45-47, and 49 are rejected under 35 U.S.C. 103(a), as being unpatentable over Foulkes *et al.* in view of Smart *et al.*

Other than reiterating the previous rejection, in the "Response to Arguments" section, the Office Action alleges that Applicants use an inaccurate analogy to sugar, while "the proper analysis involves using the references."

The Office Action suggests that "Foulkes is directed towards generically detecting compounds of interest by screening for reporter gene activity. An ordinary practitioner would be motivated by Smart to focus the broad screening method of Foulkes onto morphogenic compounds since Smart teaches 'The invention features a method of screening candidate compounds for the ability to modulate the effective local or systemic concentration or level of

morphogenic protein in an organism. (see column 2, lines 61-64).' This is an express teaching to screen for morphogenic compounds."

This argument fails to recognize the distinction between "morphogenic compounds" and "morphogen-stimulating compounds." As argued before, the combination of Foulkes and Smart would indeed lead a skilled artisan to look for agents that stimulate morphogen expression. However, this is not what is claimed. The claimed invention actually teaches a skilled artisan to by-pass morphogens, and look for morphogen analogs or replacements. The prior art is analogous to finding an agent that can stimulate insulin production, while the claimed invention is analogous to finding an insulin analog (that functions like an insulin). The former would not work in a Type I (or insulin-dependent) diabetic patient who could not make insulin himself, while the latter might work in the same patient since it does not require the patient to make his own insulin – an insulin analog could act on the same insulin receptor and perform the functions of insulin itself.

Thus these two approaches are fundamentally independent of one another, and one cannot render the other legally obvious. The concept of identifying morphogen analogs was never mentioned or suggested in either Smart or Foulkes. Thus, even assuming for the sake of argument that a skilled artisan would be motivated to combine the two references, the artisan would still not arrive at the claimed invention of identifying compounds that themselves induce a morphogen-mediated biological effect. And it naturally follows that the skilled artisan would not have a reasonable expectation of success of arriving at the claimed invention.

Thus Applicants reiterate that all elements for establishing a *prima facie* case of obviousness are not present. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection to claims 1-3, 6, 9, 13, 36, 43-47, and 49 under 35 U.S.C. 103(a) depends on combined teaching of Foulkes and Smart, further in view of Nadal-Ginard. Since Nadal-Ginard does not overcome the defects of the combined teachings of Foulkes and Smart, the combined teachings of all three references still fail to arrive at the claimed invention.

Similarly, rejection to claims 1, 13, 36, 43, and 45-50 under 35 U.S.C. 103(a) depends on combined teaching of Foulkes and Smart, further in view of Ozkaynak. Since Ozkaynak does not overcome the defects of the combined teaching of Foulkes and Smart, the combined teachings of all three references still fail to arrive at the claimed invention in the absence of a showing that the biological effect is a "morphogen-mediated" one.

Thus Applicants reiterate that all elements for establishing a *prima facie* case of obviousness are not present. Reconsideration and withdrawal of this rejection under 35 USC 103(a) are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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